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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,308	01/29/2004	Rosana Kapeller-Libermann	MPI99-193CN2M	5472

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MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
Cambridge, MA 02139

EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/767,308

Applicant(s)

KAPELLER-LIBERMANN ET AL.

Examiner

Richard Schnizer, Ph. D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 12-14, 19 and 23 is/are rejected.
- 7) ☐ Claim(s) 15-17 and 20-22 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/29/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This is a continuation of 10/056,253 (abandoned) which is a continuation of 09/443,795, now US Patent 6,383,780.

A preliminary amendment was received and entered on 1/29/04. Claims 1-11 were canceled and claims 12-23 were added as requested.

Claims 12-23 are pending and under consideration in this Office Action.

Information Disclosure Statement

An information disclosure statement was received and entered on 1/29/04. Citation numbers CA, CB, CE, CK, CL, CM, CO, and CR are incomplete because they lack publication dates. These references were considered, but cannot be published as citations unless they are corrected. Submission of a corrected IDS is suggested.

Drawings

The drawings filed 1/24/02 are acceptable for the purpose of examination.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed

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to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 4, line 24, page 9, line 25 discloses amino acid sequences in excess of 3 amino acids that are not accompanied by a SEQ ID NO.**

If these sequences are listed in the current Sequence Listing, then the specification should be amended to reflect this, if these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Objections

Claim 18 is objected to because it contains the acronym ATCC. Applicant should amend the first claim containing a given acronym to contain the full name of what is implied by the acronym. For example, claim 18 should be amended to contain the full name "American Type Culture Collection", and to include the acronym ATCC parenthetically after the full name.

Claims 21 and 23 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 21 is drawn to the polypeptide of claim 16, further comprising heterologous amino acid sequences. However, claim 16 is drawn to a polypeptide consisting of SEQ ID NO:1. Due to the closed language employed in claim 16 (consisting of), this claim does not allow for addition of any sequence to SEQ ID NO:1. So, claim 21 adds further matter to claim 16, instead of further limiting it.

Similarly, claim 22 is drawn to the polypeptide of claim 18, further comprising heterologous amino acid sequences. However, claim 18 is drawn to a polypeptide which is encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession No PTA-2811. Claim 18 does not allow for further modification of the polypeptide, so claim 21 adds further matter to claim 18, instead of further limiting it.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 12-14, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-23 are directed to polypeptides with any aminopeptidase activity, wherein the polypeptide:

- comprises an amino acid sequence at least 90% identical to SEQ ID NO:1, (claims 12, 13, and 19),
- comprises an amino acid sequence encoded by a nucleic acid at least 90% identical to SEQ ID NO:2, (claims 12 and 19),
- comprises an amino acid sequence encoded by a nucleic acid molecule that hybridizes to the complement of SEQ ID NO:2 under particular conditions set forth in claim 12, or
- comprises an amino acid sequence at least 95% identical to SEQ ID NO:1, (claims 12 and 14).

SEQ ID NO:1 is an aminopeptidase B (ApB). The prior art teaches that these enzymes catalyze the removal of N-terminal arginine and lysine residues. See Fukasawa et al (J. Biol. Chem. 271(48): (1996), page 30731, column 1, lines 5-10).

A wide variety of aminopeptidases is known in the art, and these enzymes catalyze different reactions. For example, the specification exemplifies amino peptidases that remove N-terminal methionines as well as aminopeptidases that are specific for arginine, leucine, and D-amino acids (see page 2, lines 9-14). It is clear to those of ordinary skill in the art that the specificity of a given aminopeptidase is dependent on its structure. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As such one of skill in the art could not conclude that Applicant was in possession of the genus of polypeptides comprising 90%-95% sequence identity to SEQ ID NO:1, **and** the ability to cleave any N-terminal amino acid from any polypeptide.

Enablement

Claims 12-14, 18, 19, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides comprising SEQ ID NO:1 or fragments of SEQ ID NO:1, wherein the fragments have the amino peptidase activity of SEQ ID NO:1, does not reasonably provide enablement for sequence variants of SEQ ID NO:1, or sequence variants of fragments of SEQ ID NO:1, wherein the variants have any aminopeptidase activity broadly. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 12 and 19 are drawn in part to polypeptides with aminopeptidase activity that are encoded by nucleic acid sequences that are at least 90% identical to the nucleic acid sequence of SEQ ID NO:2. SEQ ID NO:2 is a 2459 nucleotides in length, so the claims allow 246 nucleotide alterations in SEQ ID NO:2. SEQ ID NO:2 encodes a polypeptide of 650 amino acids. If each nucleotide alteration occurred in the second base of a codon in the open reading frame of SEQ ID NO:2, then the resulting polypeptides would be only 62% identical to SEQ ID NO:1. Similarly, nucleic acids that hybridize under the conditions recited in claim 12 would encode a variety of polypeptides with identities to SEQ ID NO:1 of far less than 100%.

Claims 13 and 14 are drawn to polypeptides that are 90 or 95% identical to SEQ ID NO:1.

The prior art teaches a polypeptide, rat aminopeptidase B, that is 88.6% identical to SEQ ID NO:1. See Fukasawa et al (J. Biol. Chem. 271(48): (1996). Fukasawa et al (Biochem J. 339: 497-502, 1999) taught that aminopeptidase B is a zinc metalloprotease comprising a characteristic HEXXH₁₈E zinc binding motif. Fukasawa (1999) showed that mutations in this region can interfere with catalysis. Specifically, H324Y, E325A, H328Y, and E347A mutations inactivate the aminopeptidase, whereas S327A decreases catalysis by about 15%. Y408F, N409S, and N409S/E410S mutations are not located in the active site but interfere with catalysis without completely inactivating the enzyme. See e.g. Table 2 at page 499. The specification identifies

three active site segments, KKK from positions 161-163, the HEXXHX₁₈E motif from 325-348, and a KGFCFVSYL moiety from 418-425. The rationale for the assignment of the KKK and KGFCFVSYL sequences as active site regions is unclear as these are identified by the prosite analysis in Fig. 4 as an amidation site and a putative RNA binding region, respectively. The specification provides general guidance as to what amino acid substitutions are deemed conservative in Table 1 at page 13 of the specification. No specific guidance is provided with regard to what specific amino acid substitutions are allowed at which positions, and no working example of any substitution mutation is provided. So, the prior art identifies as many as 20 single positions that can be mutated without eliminating catalysis, and one mutation in which 2 positions can be changed simultaneously, providing support for the position that at least 0.3% (2/650) of the amino acid positions in the protein can be simultaneously altered without eliminating aminopeptidase activity. In contrast, the instant claims would allow as much as 38% of amino acids to be altered simultaneously.

The prior art teaches that the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm

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for predicting the structure of a given protein from its amino acid sequence alone.

Decades of research have failed to produce such an algorithm". One might argue that it would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the cited art indicate that the effects of mutations on protein structure are unpredictable and must be determined empirically. The prior art provides limited specific guidance as to which residues of an aminopeptidase B can be substituted and which cannot, but the few residues for which there are data fall far short of the extensive modifications that are embraced by the instant claims.

It interesting to note that Fukasawa (1999) recognized a high degree of homology between rat aminopeptidase B (ApB) and leukotriene A4 hydrolase (LTA4), an enzyme with both aminopeptidase and epoxide hydrolase activities. However, despite the fact that rat ApB was more closely related to LTA4 than to any other aminopeptidase family member, Fukasawa showed that rat ApB had no epoxide hydrolase activity. Furthermore, when site directed mutations were made to the rat ApB to render it more similar to LTA4, these changes failed to produce epoxide hydrolase

activity in the resulting enzymes. This provides further evidence of the unpredictability of protein structure/function relationships.

Finally, the claims broadly polypeptides with **any** aminopeptidase activity. As noted above under Written Description, the prior art teaches that aminopeptidase B enzymes catalyze the removal of N-terminal arginine and lysine residues, whereas there are many other aminopeptidases that have different specificities owing to different three-dimensional structures. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As noted above the relationship between protein structure and function is complex and unpredictable. Absent guidance in the specification, one of skill in the art could not make fragments and variants of SEQ ID NO:1 that provide aminopeptidase activity other than that comprised by SEQ ID NO:1, without undue experimentation.

In view of the unpredictable nature of the protein structure/function relationships in general, the scarcity of data concerning aminopeptidase B structure and function, the lack of guidance or working examples in the specification regarding which amino acid residues can be substituted and which cannot while preserving aminopeptidase activity, and the lack of guidance concerning how to confer on SEQ ID NO:1 fragments and variants aminopeptidase activity other than ApB activity, one of skill in the art could not make the invention as claimed without undue experimentation.

It is further noted that the claims are drawn in part to an isolated polypeptide encoded by the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession No. PTA-2811. The specification states that the deposit will be maintained under the terms of the Budapest treaty (page 10 lines 20-24). However, the specification does not disclose what sequence is encoded by this DNA insert, and does not provide a repeatable method for obtaining the material of the deposit. Because the plasmid is essential to the claimed inventions, it must be obtainable by a repeatable method set forth in the specification of otherwise readily available to the public, or there is a failure to meet the enablement requirement. Deposit of biological material with a depository recognized under the Budapest Treaty is not sufficient assurance that all of the conditions of 37 C.F.R. 1.801-1.809 have been met. If the deposit was made under the conditions of the Budapest Treaty, then filing of an affidavit or declaration by Applicants or Assignees, or a statement by an attorney of record over his or her signature and registration number, stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when a deposit is made under the provisions of the Budapest Treaty as the treaty leaves this specific matter to the discretion of each State.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-14 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Belhacene et al (Eur. J. Immunol. 23 (8), 1948-1955 (1993)) as evidenced by NCBI output retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=Protein&list_uids=40316915&dopt=GenPept on 8/25/05.

Belhacene taught a purified human aminopeptidase B. See abstract. Absent evidence to the contrary, the polypeptide of Belhacene has the sequence attributed to it in the attached NCBI output (gi:40316915), which cites Belhacene. The polypeptide in the NCBI output is 99% identical to SEQ ID NO:1. See alignment below. The “heterologous amino acid sequences” of claim 19 are considered to be those sequences in gi:40316915 that include the amino acids that differ from SEQ ID NO:1, i.e. any sequences including position 60 or position 645.

Thus Belhacene anticipates the claims.

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ALIGNMENT FOR INSTANT SEQ ID NO:1 AND gi:40316915

"query" = SEQ ID NO:1

"Sbjct" = gi:40316915

gi|40316915|ref|NP_064601.3| **G** arginyl aminopeptidase (aminopeptidase B)
[Homo sapiens] Length=650

Score = 2104 bits (4955), Expect = 0.0

Identities = 648/650 (99%), Positives = 649/650 (99%), Gaps = 0/650 (0%)

Query	1	MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS	60
		MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS	
Sbjct	1	MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS	60
Query	61	GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPEPVSFYTQPF SHYGQ	120
		GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPEPVSFYTQPF SHYGQ	
Sbjct	61	GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPEPVSFYTQPF SHYGQ	120
Query	121	ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGGQAVLNRAFFP	180
		ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGGQAVLNRAFFP	
Sbjct	121	ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGGQAVLNRAFFP	180
Query	181	CFDTPAVKYKYSALI EVPDGFTAVMSASTWEKRGPNKFFFQMCQPI PSYLIALAIGDLVS	240
		CFDTPAVKYKYSALI EVPDGFTAVMSASTWEKRGPNKFFFQMCQPI PSYLIALAIGDLVS	
Sbjct	181	CFDTPAVKYKYSALI EVPDGFTAVMSASTWEKRGPNKFFFQMCQPI PSYLIALAIGDLVS	240
Query	241	AEVGPRSRVWAEPCLI DAANEYNGVIEEFLATGEKLF GPYVWGRYDLLFMPPSF PFGGM	300
		AEVGPRSRVWAEPCLI DA EEYNGVIEEFLATGEKLF GPYVWGRYDLLFMPPSF PFGGM	
Sbjct	241	AEVGPRSRVWAEPCLI DAAKEEYNGVIEEFLATGEKLF GPYVWGRYDLLFMPPSF PFGGM	300
Query	301	ENPCLTFVTPCLLAGDRSLADV I IHEI SHSWFGNLVTNANWGEFWLNEGFTMYAQRRI ST	360
		ENPCLTFVTPCLLAGDRSLADV I IHEI SHSWFGNLVTNANWGEFWLNEGFTMYAQRRI ST	
Sbjct	301	ENPCLTFVTPCLLAGDRSLADV I IHEI SHSWFGNLVTNANWGEFWLNEGFTMYAQRRI ST	360
Query	361	ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKL RVKIEPGVDPDDTYNETPYEKGFCF	420
		ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKL RVKIEPGVDPDDTYNETPYEKGFCF	
Sbjct	361	ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKL RVKIEPGVDPDDTYNETPYEKGFCF	420
Query	421	VSYLHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDI I PGFEFD	480
		VSYLHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDI I PGFEFD	
Sbjct	421	VSYLHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDI I PGFEFD	480
Query	481	RWLNTPGWPPYLPDLSPGDSL MKPAEELAQ LWAAEELDMKAI EAVAI SPWKTYQLVYFLD	540
		RWLNTPGWPPYLPDLSPGDSL MKPAEELAQ LWAAEELDMKAI EAVAI SPWKTYQLVYFLD	
Sbjct	481	RWLNTPGWPPYLPDLSPGDSL MKPAEELAQ LWAAEELDMKAI EAVAI SPWKTYQLVYFLD	540
Query	541	KILQKSPLPPGNVKKLGDTYPSI SNARNAELRLRWGQI VLKNDHQEDFWKVKEFLHNQ GK	600
		KILQKSPLPPGNVKKLGDTYPSI SNARNAELRLRWGQI VLKNDHQEDFWKVKEFLHNQ GK	
Sbjct	541	KILQKSPLPPGNVKKLGDTYPSI SNARNAELRLRWGQI VLKNDHQEDFWKVKEFLHNQ GK	600
Query	601	QKYTLPLYHAMMGGSEVAQT LAKETFASTASQLHSNVVNYVQQI IAPKGS	650
		QKYTLPLYHAMMGGSEVAQT LAKETFASTASQLHSNVVNYVQQI +APKGS	
Sbjct	601	QKYTLPLYHAMMGGSEVAQT LAKETFASTASQLHSNVVNYVQQI IAPKGS	650

Conclusion

No claim is allowed.

Claims 15-17 and 20 are objected to because they depend from a rejected claim but would be allowable if rewritten as independent claims including all of the limitations of the claims from which they depend. Claims 21 and 22 are objected to because they depend from a rejected claim but would be allowable if amended to overcome the objections set forth above on page 3, and if rewritten as independent claims including all of the limitations of the claims from which they depend. for the same reasons as well as those set forth above.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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A handwritten signature in black ink, appearing to read 'R. Schnizer', with a long horizontal flourish extending to the right.

Richard Schnizer, Ph.D.